Synthesis, applications and mechanistic investigations of C_2 Symmetric Guanidinium salts

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Abstract
The Guanidinium catalysts **7a-e** were prepared and applied to the phase transfer alkylation of glycinate Schiff's base **8** in 21-86% ee in addition to the phase transfer epoxidation of the chalcones **10a-e** in 85-94% ee. The pK_a values of **7a-d** were determined to be in the range 13.2-13.9, which supports a standard phase transfer mechanism for these processes. The use of **7a** and **7e** as catalysts for the addition of nucleophiles in Michael addition reactions was investigated and both were found to be effective catalysts. A counterion effect was apparent in these reactions, however no enantiomeric enrichment of the adducts was observed.

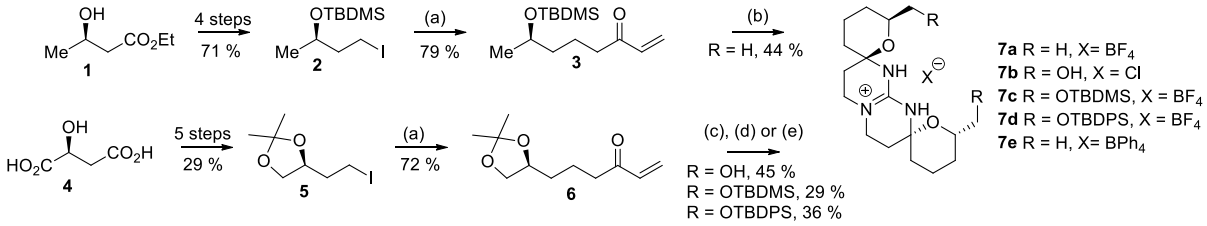
Key Words
Guanidine, Guanidinium ions, catalysis, phase transfer alkylation, phase transfer epoxidation, Michael addition.

Introduction

The guanidine motif is ubiquitous in nature and the protonated guanidinium side chain of the amino acid, arginine, leads to key highly selective hydrogen-bonding and electrostatic interactions with carboxylate and phosphate anionic groups.[1] Many applications of guanidines in synthesis[2] are known and their use as Brønsted base catalysts have been reported.[3] More recently applications of guanidines and protonated guanidines as either bases or hydrogen bond donors in bifunctional organic catalysis have also been reported.[4] We have previously reported the application of C_2 symmetric guanidinium salts in phase transfer catalysis, and in Michael additions, and report our findings in more detail.

Preparation of guanidine catalysts 7a-d

Previously[5] we reported the synthesis of the tetracyclic C_2-symmetric guanidines **7a-d** by the conjugate addition of guanidine to the enones **3** and **6**. These enones were prepared from either ethyl *R*-3-hydroxybutyrate **1** or (*S*)-malic acid **4** in 5 and 6 steps respectively. (Scheme 1)

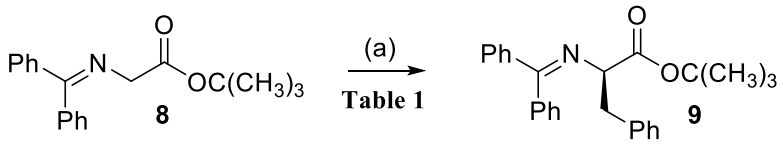


Scheme 1 (a) i) $CH_3COCHPPh_3$, *n*BuLi, ii) CH_2O. (b) i) guanidine/DMF, ii) HCl/MeOH, iii) $NaBF_4$ (aq). (c) i) guanidine/DMF, ii) HCl/MeOH. (d) As (c) then i) TBDMSCl, imidazole, DMF, ii) $NaBF_4$ (aq). (e) As in (c) then i) TBDPSCl, imidazole, DMF ii) $NaBF_4$ (aq).

The key reaction in both of these syntheses is the conjugate addition of guanidine to 2 equivalents of the enones **3** or **6**, which proceeds in good yield and gives the products **7a** and **7b**, respectively. In the case of the parent catalyst **7a**, the conjugate addition product was easily purified by column chromatography and crystallization from ether/petrol. The hydroxyl substituted catalyst **7b** was found to be very hygroscopic and was thus converted to the silyl-protected catalysts **7c** and **7d** in reasonable overall yield. Catalyst **7e** was prepared by ion exchange of **7a** with $NaBPh_4$.

Phase transfer alkylation and epoxidation reactions

With the catalysts **7a-d** in hand, we were interested in the applications of these catalysts to phase transfer catalysis (PTC)[6] and firstly investigated the benzylation of the glycinate Schiff's base **8**[7] leading to the alkylated product **9**. (Scheme 2, Table 1)



Scheme 2: (a) Catalyst 7, (0.1 eq.), NaOH (2 M), BnBr (2 eqv), CH_2Cl_2, 16 h 0 ºC-rt

Table 1

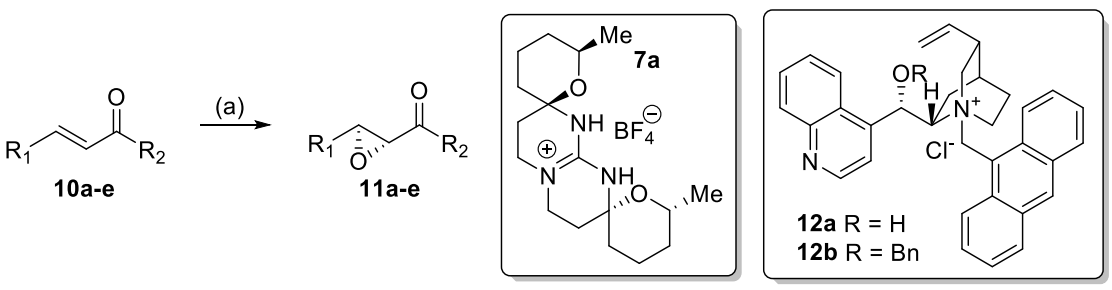
Entry	Catalyst 7	% Conv.	ee[i]
1	**7a**	>97%	86% (*R*)
2	**7b**	15%	21% (*R*)
3	**7c**	70%	65% (*R*)
4	**7d**	80%	74% (*R*)

i ± 3%

From these results it was apparent that the catalyst **7a** is the best catalyst for this

transformation effecting nearly complete conversion of **8** to the desired product **9**, which was obtained as the *R*-enantiomer in 86% ee. The catalyst **7b** gave the worst results with very low conversion and low ee, which can be attributed to its poor solubility in the organic phase of the reaction. The silyl protected catalysts **7c** and **7d** gave a lower percentage conversion however, still gave the alkylated products as the *R*-enantiomer in good ee, 65% and 74% respectively. The conversion rates for **7c** and **7d** could be raised to quantitative by increasing the concentration of sodium hydroxide in the reaction, or by allowing the reaction to progress for longer, however, this did not increase the ee of the product. The catalysts **7a, 7c** and **7d** are tolerant to these reaction conditions, may be removed from the reaction mixtures during isolation and purification of the product and can then be recycled by repeating the fluoroborate ion exchange steps of their preparation (Schemes 1). Our results and the selectivities observed are in agreement with the reactions reported by Nagasawa using structurally similar pentacyclic guanidine catalysts.[8]

We next focused on the application of **7a** to the PTC epoxidation of chalcones **10a-e**[9] (Scheme 3) and found it to be an excellent catalyst for this transformation. We initially investigated the epoxidation of chalcone **10a** (R_1 = R_2 = Ph) with NaOCl and found that the catalyst was effective over a range of 0.1 to 0.025 equivalents and gave the chalcone epoxide **11a** in consistent ee and in high yields (Table 2, entries 1-3). We wished to see if changes in the counter-ion of the hypochlorite had any effect on the ee or effectiveness of the process and thus investigated the use of LiOCl and KOCl in the reaction (both generated by the addition of the corresponding alkali metal salt to TCCA[10]). In both cases the reaction was slower and generally needed 0.1 equivalents of **7a** to effect complete conversion, however, the ees of the products were in accordance with those observed with NaOCl (entries 4 and 5). A reaction was also performed using TCCA/NaOH (entry 3), which was again correspondingly slower and required a higher catalyst loading, however, gave a comparable ee. The reason for the slower rate of reaction was unclear, and the method for the generation of the hypochlorite might be the cause. Following this, a series of chalcones **10b-e** (entries 6-9) were investigated and in general the ee's were very good (85-94 %) however in the case of the chalcone **10e** (entry 9), this substrate proved to be unreactive to these conditions and no epoxide formation was observed. Epoxidation of **10e** under the conditions reported by Lygo[9] using catalysts **12a** (entry 10) and **12b** (entry 11) did give the desired epoxide, however, both the percentage yield and ee's were poor in contract to other examples of this reaction. This result would suggest that the presence of electron donating groups on the aromatic ketone, are detrimental to the reaction when catalysed with **7a**.

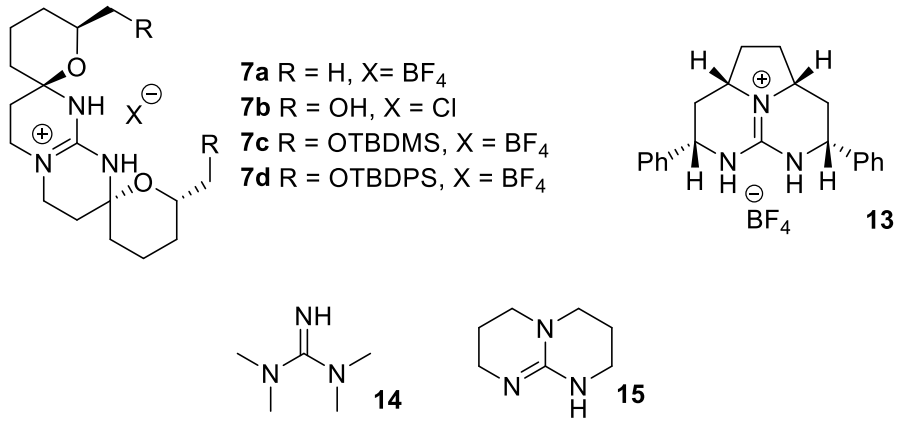


Scheme 3: (a) **7a**, **12a** or **12b** (0.1 - 0.025 eqv), MOCl (aq.), toluene, 16 - 72 h 0ºC – rt. M = Li, Na, K; R_1, R_2: See table 2

Table 2

Entry	10	R_1	R_2	M/time	Catalyst	11	Yield %	ee %	Rot
1	**10a**	Ph-	Ph-	Na 16h	**7a** (0.025 eqv)	**11a**	80	91	(−)
2	**10a**	Ph-	Ph-	Na 16h	**7a** (0.05 eqv)	**11a**	99	93	(−)
3	**10a**	Ph-	Ph-	Na 48h	**7a** (0.1 eqv)	**11a**	89	89	(−)
4	**10a**	Ph-	Ph-	K 24h	**7a** (0.1 eqv)	**11a**	73	90	(−)
5	**10a**	Ph-	Ph-	Li 72h	**7a** (0.1 eqv)	**11a**	84	92	(−)
6	**10b**	$-C_6H_{13}$	Ph-	Na 16h	**7a** (0.05 eqv)	**11b**	70	91	(−)
7	**10c**	Ph-	4-(Cl)-Ph-	Na 16h	**7a** (0.05 eqv)	**11c**	51	85	(−)
8	**10d**	4-(Cl)-Ph-	Ph-	Na 16h	**7a** (0.05 eqv)	**11d**	97	94	(−)
9	**10e**	4-(Cl)-Ph-	3,4-di(MeO)-Ph-	Na 16h	**7a** (0.05 eqv)	**11e**	0%	---	---
10	**10e**	4-(Cl)-Ph-	3,4-di(MeO)-Ph-	Na 16h	**12a** (0.06 eqv)	**11e**	51	35	(+)
11	**10e**	4-(Cl)-Ph-	3,4-di(MeO)-Ph-	Na 16h	**12b** (0.05 eqv)	**11e**	36	57	(+)

In order to probe the role of guanidinium salts **7a-e** in this reaction, we were keen to investigate the pK_as of these species. We thus determined the pK_a values for the catalysts **7a-d**, the previously prepared guanidinium salt **13**[11] and the conjugate acids of simple tetrasubstituted guanidines **14** and **15** in DMSO using a spectrophotometric method.[12] The pK_a values for **7a-d** and **13, 14** (Table 3) were all relatively similar in value in the range 13.0 - 13.9. The pK_a of the commercially available tetramethylguanidine **14** was calculated as 13.04 and was also in full agreement with the literature value of 13.0 (determined in DMSO) albeit using a different method.[14] As an internal calibration, the pK_a of acetic acid was also calculated as 12.48 using the spectrophotometric method, which is in accordance with the literature value of 12.31.[13] The small increases in pK_as between catalysts **13** and **7a-d** relative to tetramethylguanidine **14** would be expected due to the electron-donating nature of the pyran scaffold, which will stabilise the cationic guanidinium ion relative to the neutral conjugate base. As the changes in the R-substituents of **7a** – **7d** are relatively remote from the site of ionisation, it is not surprising that pK_a changes are small in this series. All of the catalysts **7a**-**7d** and **13** clearly push the indicator/guanidine equilibrium towards deprotonated indicator as higher absorbance values are observed than for tetramethylguanidine **14**, which shows an increased basicity of the catalysts. In fact, absorbance values for **7a** – **7c** and **13** are close to the A_{max} value observed for fully deprotonated indicator (the anion of 2,4-dinitrodiphenylamine). An alternative indicator with a pK_a value between that of 2,4-dinitrodiphenylamine (12.74) and 2-naphthol (17.1) in DMSO was not available to provide additional estimates of pK_as in these cases. One exception was higher pK_a value of 16.1 for the conjugate acid of 1,5,7-triazabicyclo[4.4.0]dec-5-ene **15**. This 2 pK unit difference of basicity is of interest in comparison to the catalysts **7a-d** and suggests that the pyran rings have an effect on their basicity when compared to the simple guanidines **13** and **14.**



Scheme 4

Table 3 pK_a values in DMSO for Guanidinium Salts **7a-d** and **13-15**

Entry	Compound	pK_a
1	**7a**	13.87± 0.05
2	**7b**	13.91± 0.08
3	**7c**	13.62± 0.06
4	**7d**	13.20± 0.06
5	**13**	13.69± 0.05
6	**14**	13.04± 0.05
7	**15**	16.14± 0.05
8	**Acetic acid**	12.48± 0.06

As the reactions described herein utilising catalysts **7a-d** and **13** are in mixed biphasic systems utilising non-polar toluene or DCM (x-y%) and highly polar water (10-50%), the use of pK_as measured in DMSO will be a reasonable reflection of the polarity of the solvent system.[1] The Henderson-Hasselbalch equation (**Equation 1**) relates pH to the pK_a and gives the ratio of the species in the acidic/basic forms. For the guanidinium species (**7a-d** and **13-15)** the pK_as were all above 13, and as our reactions were carried out at a pH_{obs} >12 (as determined by pH meter), the estimated levels of protonation in the guanidine/guanidinium equilibrium is > 92%. This result suggests that the guanidine salts **7a-e** are acting as a phase transfer agent under our conditions, rather than as a base or nucleophile, and a standard mechanistic rationale can be invoked.

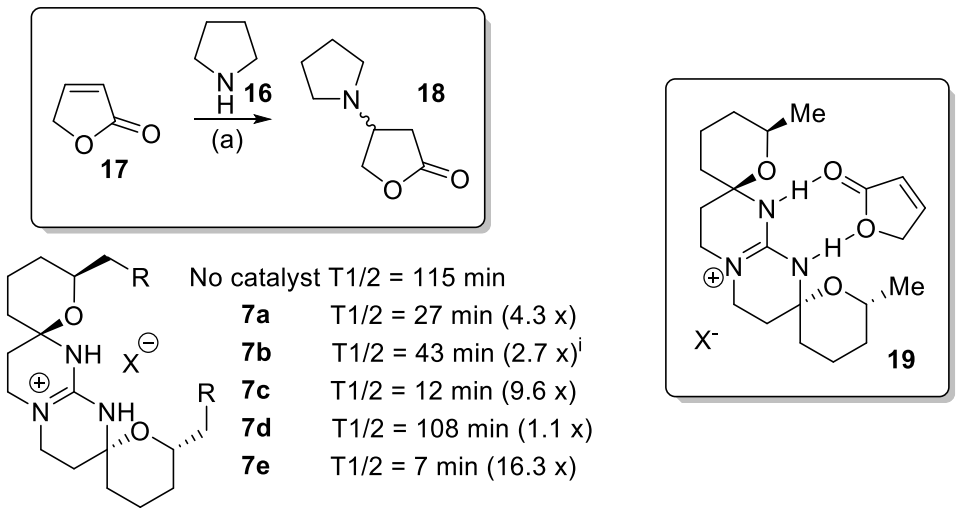
$$pH = pK_a + \log\left(\frac{[A^-]}{[HA]}\right)$$

Equation 1. The Henderson-Hasselbalch equation, relating pH to pK_a.

[1] The determination of pK_a values directly in mixed solvent, biphasic systems is challenging particularly with non-polar solvent components such as toluene and DCM.

Michael reactions

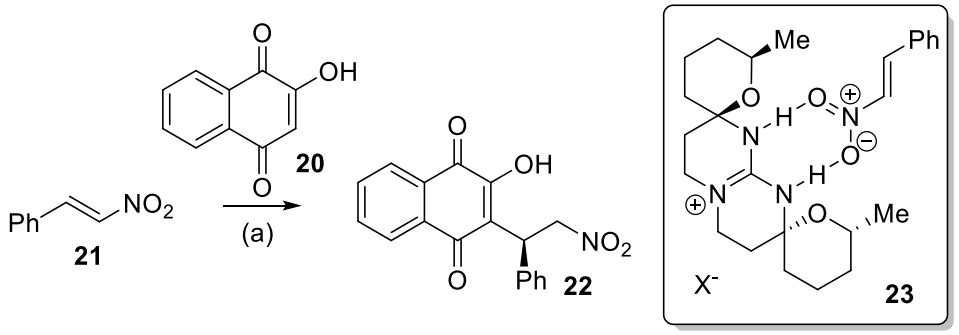
We next investigated the application of **7a-e** as catalysts for the Michael[3] reaction. We had initially investigated the application of the salt **7a** as a catalyst in the conjugate addition of pyrrolidine **16** to unsaturated lactone **17** (Scheme 5) which was reported by Mendosa.[15] We observed an increase in rate of reaction for all the guanidine salts **7a-e**. The parent catalyst **7a** gave a 4.3 fold increase in reaction rate, whilst the TBDMS-catalyst **7c** gave a 9.6 fold increase in reaction rate. A further improvement was found when catalyst **7e** was employed, in which the BF_4^- counter-ion has been exchanged for the more bulky BPh_4^-, which led to a 16.3-fold increase in reaction rate over the uncatalyzed process. The effect of the BPh_4^- counterion in this process is that it is less co-ordinating and has a decreased hydrogen bonding interaction with the guanidine, thus allowing an easier formation of the proposed intermediate **19**. Interesting the TBDPS-catalyst **7d** gave very little increase in rate possibly showing that there is an inter-play between steric bulk and lipophilicity. Disappointingly no asymmetric induction was observed in this reaction which was attributed to the site of reaction being too far removed from the point of asymmetric induction within the proposed intermediate **19**.



Scheme 5 (a) **7a-e** (0.1 eq.), 0.3 M in $CDCl_3$ (i. 20% CD_3OD was added) rt.

We also studied the reaction of 2-hydroxy-1,4-napthaquinone **20** (lawsone) with trans-β-nitrostyrene **21** as it was known that this reaction could be catalysed using a bifunctional thiophosphoramide system.[3w,x] We initially investigated the background reaction of **20** with **21** in various solvents (Scheme 6, Table 3) and found that the reaction did not occur at an appreciable rate in non-protic solutions such as THF (entry 1), however the reaction did slowly proceed in ethanol with a $T_{1/2}$ of 509 h (entry 2). It was also observed that the addition of water to the reaction solvents did accelerate the reaction, for example the addition of water (3%) to ethanol gave a 7.8 fold increase in rate (entry 3). We then investigated the use of catalyst **7a** in this reaction and found that in ethanol the reaction

proceeded slowly with a $T_{1/2}$ of 86 h (entry 4), whilst the use of catalyst **7e** (entry 5) with a bulkier counterion (BPh_4^-) gave a shorter $T_{1/2}$ at 39 h (entry 5). Switching to the non-protic solvent THF led to the complete cessation of reaction when **7a** was employed as the catalyst (entry 6), whilst catalyst **7e** (entry 7) gave a $T_{1/2}$ of 465 h (entry 7). The effect of the BPh_4^- counterion is again obvious in the increase in rate of reaction. This slower rate of reaction in THF suggested that the reaction might require a proton source we thought that the inclusion of an acid donor might accelerate the reaction and we attempted the reaction in the presence of *L*-proline. *L*-proline itself was a weak catalyst for the reaction with a $T_{1/2}$ of 579 h in THF(entry 8) and in combination with **7a** the reaction did proceed at a faster rate with a $T_{1/2}$ of 387 h (entry 9). Switching again to the catalyst **7e** with the BPh_4^- counterion again had a positive effect with the rates of reaction in the non protic solvents acetonitrile, dichloromethane and THF having $T_{1/2}$ values in the range of 80-100 h (entries 11-13). The best result observed using **7e** at a higher concentration in THF with a $T_{1/2}$ of 49 h and an overall yield of 95% after 8.5 days (entry 15). We attempted the use of *N*-methyl-*L*-proline which the slightly more basic N-Me group and found that this again worked as a catalyst with a $T_{1/2}$ of 80 h (entry 16). comment



Scheme 5 (a) **7a or 7e** (0.05 eqv.), see table 3.

Table 3

Entry	Solvent	Catalyst	Additive	$T_{1/2}$ h (d)	Conversion % (d)	Yield %
1	THF	None	None	---	<1 (71)	---
2	EtOH	None	None	509 (21)	75 (58)	---
3	EtOH	None	H_2O (3 %)	65 (2.7)	100 (30)	90
4	EtOH	**7a**	None	86 (3.6)	90 (42)	76
5	EtOH	**7e**	None	39 (1.6)	100 (20)	82
6	THF	**7a**	None	---	0 (21)	---
7	THF	**7e**	None	465 (19.4)	85 (71)	52
9	THF	None	*L*-proline	579 (24.1)[i]	45 (22)	39
10	THF	**7a**	*L*-proline	387 (16.1)[i]	46 (14)	38
11	CH_3CN	**7e**	*L*-proline	100 (4.2)	94 (28)	92
12	CH_2Cl_2	**7e**	*L*-proline	84 (3.5)	95 (6)	85
13	THF	**7e**	*L*-proline	80 (3.3)	97 (27)	77
14	THF 2[ii]	**7e**	*L*-proline	49 (2)	99 (8.5)	95
15	THF 2[ii]	**7e**	*N*-Methyl *L*-proline	80 (3.3)	70 (4.9)	65

i Estimated values. *ii* Triple concentration with respects to entry 13

Conclusion

Using a spectrophotometric method, pK_a values in the range 13.2-13.9 in DMSO have been determined for a range of chiral guanidine-derived catalysts highlighting an increase in basicity relative to achiral tetramethylguanidine (pK_a = 13.0). As these pK_a values are substantially above the observed pH values (~12) for the synthetic applications of these catalysts in biphasic media described herein, a mechanism involving the protonated guanidinium ion as a phase transfer catalyst is most likely.

Acknowledgements

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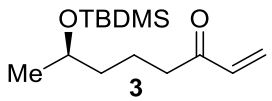
Experimental

General conditions Column chromatography was carried out on silica gel (particle size 40 to 63μm) and TLCs were conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Ether, THF and dichloromethane were dried on a Pure Solv MD-3 solvent purification system. Dry methanol and DMF was purchased from Aldrich. Chemical shifts are reported in δ values relative to chloroform (7.27/77.0 ppm) as an internal standard. Proton and carbon were recorded in $CDCl_3$ on a Bruker AC250, AC400 or AC500 spectrometer unless otherwise stated. Mass spectra data were obtained at the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea. Infrared spectra were recorded as thin films (oils) on a Bruker Tensor 27 series instrument.

(*R*)-7-oxo-((*tert*-butyldimethylsilyl)oxy)oct-1-ene-3-one **3**

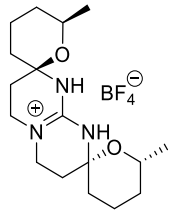


3

Acetylmethylene triphenylphosphorane (8.26 g, 28.9 mmol) was dissolved in dry THF (140 mL), cooled (–78 ºC) whereupon BuLi (2.2 M, 11.9 mL, 26.3 mmol) was added drop wise over 5 min. The deep red solution that formed was then stirred at –60 ºC for 1 h. The reaction was cooled (–78 ºC) and (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane[16] (8.26 g, 26.3 mmol) in THF (42 mL) was added and the reaction warmed to rt by removal of the cooling bath followed by stirring overnight. Water (90 mL) was added and the solution was separated and the aqueous fraction extracted with dichloromethane (3 × 50 mL), the combined extracts

dried ($MgSO_4$) and concentrated by rotary evaporation to approximately 50 mL. Formaldehyde solution was then prepared by adding aqueous formaldehyde (94 mL) to dichloromethane (100 mL) and removing the water by drying ($MgSO_4$). This dried solution was added to the reaction via a funnel containing a cotton wool plug and stirred overnight. The reaction was diluted with ether (100 mL) and washed with water (2 × 50 mL), then dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (4 % diethyl ether in petrol) gave **3** as a clear oil (5.34 g, 79%). $\mathbf{R_f}$ 0.19 (2% ethyl acetate/petrol); $\mathbf{[\alpha]_D^{25}}$ -13.4 (*c* 1.1 in $CHCl_3$); $\mathbf{\delta_H}$ 6.36 (1H, dd, *J* 17.6, 10.1 Hz, CH), 6.21 (1H, dd, *J* 17.6, 1.5 Hz, CH), 5.81 (1H, dd, *J* 10.1, 1.5 Hz, CH), 3.79 (1H, apparent sextet, *J* 6.0 Hz, CH), 2.57 (2H, t, *J* 7.3 Hz, CH_2), 1.37 - 1.73 (4H, m, 2 × CH_2), 1.14 (3H, d, *J* 6.1 Hz, CH_3), 0.88 (9H, s, 3 × CH_3), 0.05 (6H, s, 2 × CH_3); $\mathbf{\delta_C}$ 200.8, 136.5, 127.9, 68.3, 39.7, 39.1, 25.9, 23.7, 20.2, 18.1, -4.4, -4.8; $\boldsymbol{\nu}_{max}$ (neat) 2940 (C-H), 1684 (C=O), 1616 (C=C); ***m/z*** **(CI)** 257 (5% $[M+H]^+$), 201 (45% $[MH-^tBu]^+$), 132 (50%), 74 (100%); **HRMS (CI)** found 257.1937 ($[M+H]^+$), $C_{14}H_{29}O_2Si$ requires 257.1931.

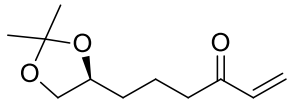
(6*R*, 6"*R*, 2*R*, 2"*R*)-6,6"-dimethyldispiro[tetrahydropyran-2,2'-(2,3,4,6,7,8- hexahydro-1H-pyrimido[1,2-a]pyrimidine)-8',2"-tetrahydropyran]-9'-ium tetrafluroborate **7a**



7a

Enone **3** (1.99 g, 7.77 mmol) was dissolved in dry DMF (35 mL), cooled (0 ºC) and a solution of guanidine (0.23 g, 3.89 mmol) in DMF (5 ml) was added drop wise over 5 min. After stirring to rt over 16 h, the reaction was cooled (0 ºC) and methanolic HCl (40 mL, prepared by the slow addition of acetyl chloride (4 mL) to cooled (0 ºC) methanol (36 mL)) was added. The reaction was allowed to warm to rt and stirred vigorously for 3 h. After dilution with dichloromethane (200 mL) the mixture was washed LiBr solution (sat. 3 × 150 mL) and water (3 × 100 mL). The aqueous washings were backwashed with dichloromethane (50 mL) and the combined organic washings were dried ($MgSO_4$) and the solvent removed by rotary evaporation until approximately 30 mL of solution remained. An aqueous solution of $NaBF_4$ (sat. 30 mL) was added and the mixture stirred overnight. After separation the organic phase was washed with water (3 × 30 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (gradient elution: chloroform to 1.5% methanol/chloroform 0.25 % steps) gave **7a** (670 mg, 44 %) as a white solid after trituration with diethyl ether. $\mathbf{R_f}$ 0.39 (5% MeOH/$CHCl_3$); $\mathbf{[\alpha]_D^{25}}$ +45 (*c* 0.65 in $CHCl_3$); **m.p.** 181-182^{o}C; $\mathbf{\delta_H}$ 7.50 (2H, br s, 2 × NH), 3.84 (2H, ddq, *J* 11.8, 6.1, 2.1 Hz, 2 × CH), 3.68 (2H, apparent dt, *J* 12.4, 5.0 Hz) 3.22 (2H, ddd, *J* 12.5, 5.8, 1.6 Hz), 1.50-2.20 (14H, m), 1.18 (2H, m, 2 × CH), 1.11 (6H, d, *J* 6.1 Hz, 2 × CH_3); $\mathbf{\delta_C}$ 148.4, 78.9, 66.9, 42.7, 33.6, 33.6, 32.1, 21.7, 17.7; $\boldsymbol{\nu}_{max}$ 3378 (bm, NH str), 3004 (C-H), 1667 (C=N), 1599 (C=N); ***m/z*** **(CI)** 308 (100% $[M+H]^+$); **HRMS (CI)** found 308.2338. ($[M+H]^+$) $C_{17}H_{30}N_3O_2$ requires 308.2333.

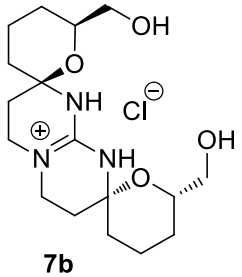
(S)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)hex-1-en-3-one **6**



6

Acetylmethylene triphenylphosphorane (2.73 g, 8.6 mmol) was dissolved in dry THF (40 mL), cooled (–70 ºC) and BuLi (2.22 M, 3.87 mL, 8.6 mmol) was then added slowly over 15 min. The reaction was then warmed and stirred for 1 h at –50 ºC then re-cooled (–78 ºC). (4*S*)-2,2-dimethyl-1,3-dioxolane-4-iodoethane[5b] (2.05 g, 7.81 mmol) was then added as a solution in THF (3 mL) and the reaction allowed to warm to rt over 12 h. Water (40 mL) was added and the mixture extracted with dichloromethane (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporator. Formaldehyde in dichloromethane (prepared by drying ($MgSO_4$) a mixture of aqueous formaldehyde (37 % w/v, 28 mL) and dichloromethane (30 mL)) was added and the reaction stirred for a further 24 h. After washing with water (2 × 30 mL), the organic fraction was dried ($MgSO_4$) and the solvent removed by rotary evaporator. The solid obtained was triturated with ether (5 × 30 mL), and the resulting oil purified by column chromatography (5% diethyl ether/petrol) to yield the desired product as an unstable clear oil (1.08 g, 72%). $\mathbf{R}_f$ 0.19 (5% diethyl ether in petrol); $\boldsymbol{\delta}_\mathbf{H}$ 6.35 (1H, dd, *J* 17.7, 10.1 Hz), 6.20 (1H, dd, *J* 17.7, 1.6 Hz), 5.83 (1H, dd, *J* 1.6, 10.1 Hz), 4.02-4.14 (2H, m, 2 × CH), 3.54 (1H, t, *J* 6.7 Hz), 2.65 (2H, t, *J* 7.0 Hz, CH_2), 1.85-1.52 (4H, m, 2 × CH_2), 1.40 (3H, s, Me), 1.35 (3H, s, Me); $\boldsymbol{\delta}_\mathbf{C}$ 200.3, 136.5, 128.1, 108.8, 75.8, 69.3, 32.9, 26.9, 25.7, 20.1; $\boldsymbol{\nu}_{max}$ (thin film) 2985 (C-H), 1701 (C=O), 1681 (C=C), 1369 (C-H).

(2*R*,6*S*,6"*S*,8'*R*)-6,6"-bis(hydroxymethyl)-3,3",4,4',4",5,5",6,6',6",7',9'-dodecahydro-1'H,3'H-dispiro[pyran-2,2'-pyrimido[1,2-a]pyrimidine-8',2"-pyran]-5'-ium chloride **7b**

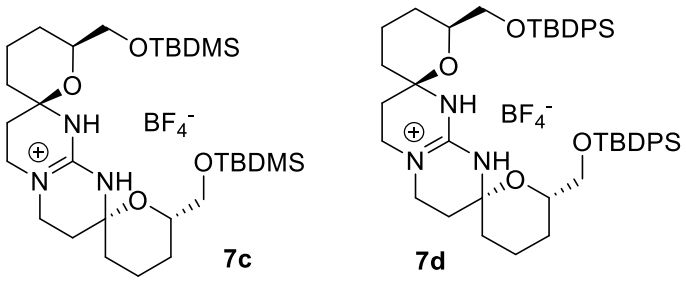


7b

A solution of guanidine (68.0 mg, 1.2 mmol) in dry DMF (5 mL) was added to a cooled (0 ºC) solution of enone **6** (0.5 g, 2.5 mmol) in dry DMF (2 mL) and the reaction warmed to rt over 24 h. The reaction was cooled (0 ºC) and methanolic HCl (7 mL, prepared from acetyl chloride (1 mL) and dry methanol (6 mL)) was then added and the reaction stirred for a further 3 h. After evaporation, column chromatography (graduated solvent system 0%, 1%, 3%, 5%, 10%, 15%, 20%, 40% MeOH in $CHCl_3$) followed by collecting of the fractions eluting at 15-20 % gave **7b** (0.23 g, 45 %) as a highly hygroscopic solid. $\mathbf{R}_f$ 0.17 (15% MeOH/$CHCl_3$); $\boldsymbol{[\alpha]}_\mathbf{D}^{\mathbf{25}}$ + 28 (*c* 0.5, MeOH). $\boldsymbol{\delta}_\mathbf{H}$ 3.74-3.92 (4H, m, 2 × CH_2), 3.52-3.63 (4H, m, 2 × CH_2), 3.35-3.50 (2H, m, 2 × CH), 1.70-2.20 (14H, m), 1.35-1.55 (4H, m, 2 × CH_2); $\boldsymbol{\delta}_\mathbf{C}$

151.2, 81.2, 74.0, 67.3, 44.6, 35.9, 34.7, 28.6, 20.1; ***m/z*** **(CI)** 340.2 (100% $[M+H]^+$); **HRMS(EI)** found 340.2236, $C_{17}H_{30}N_3O_4$ ($[M]^+$) requires 340.2236.

(2R,6S,6"S,8'R)-6,6"-bis(((isopropyldimethylsilyl)oxy)methyl)-3,3",4,4',4",5,5",6,6',6",7',9'-dodecahydro-1'H,3'H-dispiro[pyran-2,2'-pyrimido[1,2-a]pyrimidine-8',2"-pyran]-5'-ium tetrafluoroborate **7c** and (2R,6S,6"S,8'R)-6,6"-bis(((tert-butyldiphenylsilyl)oxy)methyl)-3,3",4,4',4",5,5",6,6',6",7',9'-dodecahydro-1'H,3'H-dispiro[pyran-2,2'-pyrimido[1,2-a]pyrimidine-8',2"-pyran]-5'-ium fluoroborate **7d**

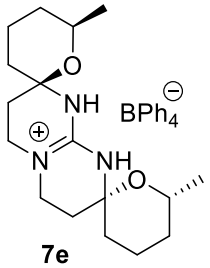


Guanidinium salt ***7d***: Guanidine (403.0 mg, 6.8 mmol) as a solution in DMF (5 mL) was added to a stirred and cooled (0 ºC) solution of enone **6** (2.84 g, 14.3 mmol) in dry DMF (64 mL) and the mixture slowly warmed to rt over 24 h. Methanolic HCl (25 mL, prepared from the addition of acetyl chloride (5 mL) to cooled dry methanol (20 mL)) was added and the mixture stirred for a further 4 h. The solvent was removed under reduced pressure and the resulting oil purified by column chromatography (gradient elution in $CHCl_3$ then 3%, 5%, 10%, 15%, 20% and 50% MeOH in $CHCl_3$) with the fraction eluted at 10% being collected. These fractions were then dissolved in dry DMF (20 mL), cooled (0^oC) and TBDMSCl (3.1 g, 20.6 mmol) and imidazole (1.87 g, 27.5 mmol) added. After stirring to rt over 24 h the reaction was diluted with dichloromethane (100 mL) and washed with water (5 × 30 mL), LiBr solution (aq. sat., 30 mL) and water (30 mL) then dried ($MgSO_4$). The organic phase was evaporated to ca. 30 mL and a solution of $NaBF_4$ (sat., 30 mL) added and the mixture stirred for 16 h. The organic phase was separated, washed with water (3 × 30 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (gradient elution in $CHCl_3$ then 0.5%, 1%, 2%, 5%, 10% and 20% MeOH in $CHCl_3$) collecting the fractions eluting in 1-5 % MeOH in $CHCl_3$ gave **7c** (1.31 g, 29 %) as an amorphous white solid. **7c** $\mathbf{R_f}$ = 0.35 (4% MeOH in $CHCl_3$); $\mathbf{[\alpha]_D^{25}}$ + 47 (*c* 0.5 in $CHCl_3$); **m.p.** 207-209 ºC; $\mathbf{\delta_H}$ 7.45 (2H, br s, NH), 3.85-3.66 (4H, m, 2 × CH_2), 3.51 (4H, d, *J* 5.0 Hz, 2 × CH_2), 3.18 (2H, dd, *J* 12.3, 5.2 Hz, 2 × CH), 1.54-2.00 (14H, m) 1.19-1.34 (2H, m, 2 × C*H*H), 0.85 (18H, s, 6 × CH_3), -0.03 (12H, s, 4 × CH_3); $\mathbf{\delta_C}$ 148.5, 80.6, 78.9, 71.8, 66.3, 44.9, 33.8, 33.0, 26.2, 25.8, 18.2, 17.1, -5.3; $\mathbf{\nu}_{max}$ ($CHCl_3$) 3370 (N-H), 2953 (C-H), 1660 (N-H) cm^{-1}; **HRMS(EI)** found 567.3876, $C_{29}H_{57}N_3O_4Si_2$ ($[M]^+$) requires 567.3888.

Guanidinium salt ***7d***: This was prepared in an identical manner from enone **6** (2.97 g, 15.0 mmol), guanidine (400.0 mg, 6.8 mmol), TBDPSCl (5.61 g, 20.4 mmol) and imidazole (1.87 g, 27.2 mmol). Purification by column chromatography (gradient elution in $CHCl_3$ then 2%, 3%, 4%, 5%, 10%, 15% and 20% MeOH in $CHCl_3$) collecting the fractions eluted at 4-5 %

MeOH in $CHCl_3$ gave **7d** (2.21 g, 36 %) as an amorphous white solid. **7d** $\mathbf{R_f}$ = 0.29 (4% MeOH in $CHCl_3$); $\mathbf{[\alpha]^{25}}$ + 44 (*c* 0.5 in $CHCl_3$); **m.p.** 200 ^oC; $\mathbf{\delta_H}$ 9.48 (2H, br s, NH), 7.71-7.64 (8H, m, 8 x CH), 7.44-7.34 (12H, m, 12 x CH), 3.94-4.05 (2H, m, 2 × CH), 3.69-3.53 (6H, m, 2 × CH_2, 2 x CH), 3.02 (2H, dd, *J* 5.3, 11.7 Hz, 2 × CH), 2.65-2.41 (2H, m), 1.97-1.50 (12H, m, 6 × CH_2), 1.40-1.15 (2H, m), 1.02 (18H, s, 2 × *t*Bu); $\mathbf{\delta_C}$ 148.3, 135.4, 135.4, 133.5, 133.4, 129.6, 129.5, 127.5, 78.7, 71.6, 66.7, 42.7, 33.5, 32.8, 26.0, 26.0, 19.1, 17.0; $\mathbf{\nu}_{max}$ (in $CHCl_3$) 3360 (N-H), 2947 (C-H), 1664 (N-H); **HRMS(EI)** found 816.4583, $C_{49}H_{66}N_3O_4Si_2$ ($[M+H]^+$) requires 816.4592.

(*6R*, *6″R*, *2R*, *2″R*)-6,6″-Dimethyldispiro [tetrahydropyran-2,2'-(2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-a] pyrimidine)-8',2″-tetrahydropyran]-9'-ium tetraphenylborate **7e**



7e

The reaction for the preparation of **7a** was repeated with the omission of the final wash with $NaBF_4$ solution. Purification of the residue obtained by column chromatography gave the corresponding guanidinium chloride (199.7 mg, 0.581 mmols) which was dissolved in dry THF (5 mL) and $NaBPh_4$ (0.6 g, 1.75 mmols) was added. After stirring this mixture for 6 h, the solvent was removed *in vacuo* and the white solid obtained dissolved in dichloromethane (20 mL) and washed with H_2O (2 × 50 mL) to remove NaCl and excess $NaBPh_4$. The solution was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give **7e** as a white solid (321.8 mg, 0.513 mmols) in 88 % yield. $\mathbf{[\alpha]^{27}}$ + 67 (*c* 0.5 in $CHCl_3$); m.p. 63-65 ºC (dec.); $\mathbf{\delta_H}$ 7.48 - 7.54 (8H, m, 8 × ArH), 7.07 (8H, app t, *J* 7.4 Hz, 8 × ArH), 6.93 (4H, t, *J* 7.2 Hz, 4 × ArH), 6.31 (2H, br s, 2 × NH), 3.41 - 3.52 (4H, m, 4 × CH), 2.92 (2H, dd, *J* 12.4, 5.5 Hz, 2 × CH), 1.78 (2H, dd, *J* 13.5, 4.3 Hz, 2 × CH), 1.26 - 1.58 (14H, m), 1.11 (6H, d, *J* 6.1 Hz, 2 × CH_3); $\mathbf{\delta_C}$ 164.7, 164.4, 164.0, 163.6, 148.0, 136.0, 125.8, 121.9, 79.0, 67.0, 42.7, 33.3, 32.8, 32.0, 21.7, 18.0; $\mathbf{\delta_B}$ -6.46. **HRMS (CI)** found 308.2332. ($[M+H]^+$) $C_{17}H_{30}N_3O_2$ requires 308.2333; found 319.1660 ($[M]^-$) $C_{24}H_{20}B$ requires 319.1664.

General method for glycinate Schiff's base reactions

The guanidinium salt **7a-e** (0.04 mmol) and the glycinate Schiff's base **8** (120 mg, 0.407 mmol) were dissolved in dichloromethane (2 mL) and aqueous NaOH solution (2 mL, 2M), was added. This mixture was cooled (0 ºC), vigorously stirred and BnBr (139 mg, 0.814 mmol, 120 μL) was then added in one portion. After stirring to rt over 16 h, dichloromethane (15 mL) was added and the organic layer separated, dried ($MgSO_4$) and evaporated, then purified by column chromatography (diethyl ether/petrol). Conversion rates were determined by ^1H nmr and ee's (+/- 3%) were determined on a Bakerbond DNPG column (98.5:1.5

hexane:dioxane).

General method for phase transfer epoxidation of chalcones 10a-e
Using Sodium hypochlorite solution: The guanidinium salt **7a-e** (0.025-0.10 eqv.) and the chalcone **10a-e** (1.04-1.60 mmol) were dissolved in toluene (2-3 mL) and the mixture cooled (0 ºC) and stirred vigorously. Sodium hypochlorite solution (8% aqueous solution, 3 eqv.) was then added and the reaction stirred to rt over 16 h. Dichloromethane (15 mL) was added and the organic layer separated, dried ($MgSO_4$) and evaporated. Purification by chromatography eluting with diethyl ether and petrol gave **11a-e**. Enantiomeric excesses (+/- 3%) were determined on a Chiralpak AD column (see supporting information).

Using TCCA/MOH: Chalcone **10a** (100 mg, 0.48 mmol) and the catalyst **7a** (18.8 mg, 0.048 mmol, 0.1 eqv) were dissolved in toluene (3 mL) and cooled (0 ºC). TCCA (74.5 mg, 0.32 mmol, 0.67 eqv.) was then added ensuring full dissolution. If full dissolution did not occur additional toluene (1-2 mL) was added. The required alkali metal hydroxide solution (KOH (18 M, 0.27 mL), NaOH (18 M, 0.27 mL) or LiOH (5.1 M, 0.94 mL), 4.8 mmol, 15 eqv.) was added drop wise and the reaction was stirred vigorously for 24 h or until the reaction had reached completion as determined by TLC. At this point ether (25 mL) and water (25 mL) were added and the organic layer separated, the aqueous layer was extracted with further ether (2 × 25 mL) and the combined extracts dried ($MgSO_4$) then passed through a short pad (ca. 2 cm) of silica gel eluting with further ether. After evaporation the resulting yellow oil was purified by column chromatography (0.5% diethyl ether in petrol to remove residual traces of chalcone then 1-3% in 0.5% increments) to give the chalcone epoxide **11a** as a white solid. Enantiomeric excesses (+/- 3%) were determined on a Chiralpak AD column (see supporting information).

General method for Michael addition of 2-hydroxy-1,4-napthaquinone 20 with trans-β-nitrostyrene 21 2-Hydroxy-1,4-napthaquinone **20** (100 mg, 0.574 mmol) and *trans*-β-nitrostyrene **21** (128.5 mg, 0.861 mmol, 1.5 eqv.) were dissolved in the required dry solvent (5-15 mL, see table 3) and the mixture cooled (0 °C). The catalyst **7a** or **7e** (0.05 eqv.) was added and the yellow reaction mixture allowed to warm to rt and stirred. The reaction was monitored by NMR and on completion the solvent was evaporated to give a deep red residue which was purified by column chromatography eluting firstly with 1-5% ethyl acetate in petrol to remove excess **21** then dichloromethane to give the product **22** as a yellow solid. In the cases where *L*-proline (0.05 eqv.) was added the catalyst was stirred with the *L*-proline for 1h at rt, before cooling whereupon **20** and **21** were added sequentially as solids. Reaction progress was determined by sampling and determination by ^1H nmr. For determination of enantiomeric excess (ee values), samples were analysed on a PerkinElmer Series 200 HPLC equipped with diode array detector monitoring at 254nm. A 20ul injection of the sample dissolved in the mobile phase was separated using a CHIRALPAK IA column (250 x 4.6mm) with 90% Hexane with 0.1% TFA, 8% Ethanol and 2% Dichloromethane as the mobile phase (see supporting information).

References

1. (a) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev*. **2003**, 240, 3–15; (b) Schug, K. A.; Lindner, W. *Chem. Rev*. **2005**, 105, 67–113; (c) Blondeau, P.; Segura, M.; Pérez-Fernández, R.; de Mendoza, *J. Chem. Soc. Rev*. **2007**, 36, 198–210; (d) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep*. **2008**, 25, 919–954.

2. For reviews on guanidines in organic synthesis, see: (a) Ishikawa, T.; Isobe, T. *Chem. Eur. J*. **2002**, 8, 552–557; (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752; (c) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, 8, 552; (d) Leow, D.; Tan, C. H. *Chem.Asian J.* **2009**, 4, 488; (e) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245; (f) Yu, Z. P.; Liu, X. H.; Zhou, L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2009**, 48, 5195; (g) Fu, X.; Loh, W. T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H. J.; Wang, J. M.; Tan, C. H. *Angew. Chem., Int. Ed.* **2009**, 48, 7387; (h) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, 49, 1858; (i) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, 132, 6286.

3. For reviews see: (a) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, 4, 488–507; (b) Alvarez-Casao, Y.; Marques-Lopez, M.; Herrera, R. P.; *Symmetry* **2011**, 3, 220–245. For examples see: (c) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, 111, 4994–4995; (d) Kurzmeier, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, 55, 3749–3755; (e) Iyer, M. S.; Gigstad, K. M. *J. Am. Chem. Soc.* **1996**, 118, 4910–4911; (f) Corey, E. J.; Grogan, J. M. *Org. Lett.* **1999**, 1, 157–160; (g) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, 128, 1454–1455; (h) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, 130, 9228–9229; (i) Jiang, Z.; Yang, Y.; Pan, Y.; Zhao, Y.; Liu, H.; Tan, C.-H. *Chem. Eur. J.* **2009**, 15, 4925–4930; (j) Lovick, H. M.; Michael, F. E. *Tetrahedron Lett.* **2009**, 50, 1016–1019; (k) Fu, X.; Loh, W.-T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2009**, 48, 7387–7390; (l) Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4014–4019; (m) Jiang, Z.; Yang, Y.; Pan, Y.; Zhao, Y.; Liu, H.; Tan, C.-H. *Chem. Eur. J.* **2009**, 15, 4925–4930; (n) Pan, Q. B.; Ma, D. W. *Chin. J. Chem.* **2003**, 21, 793–796; (o) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T.; *Chem. Commun.* **2001**, 245–246; (p) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, 73, 133–141; (q) Terada, M.; Be, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, 128, 1454–1455; (r) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, 128, 13692–13693; (s) Jiang, Z.; Ye, W.; Yang, Y.; Tan, C.-H. *Adv. Synth. Catal.* **2008**, 350, 2345–2351; (t) Ye, W.; Jiang, Z.; Zhao, Y.; Goh, S. L. M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, 349, 2454–2458; (u) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, 128, 16044–16045; (v) Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. *Eur. J. Org. Chem.* **2008**, 2759–2766. (w) Zhou, W.-M.; Liu, H.; Du, D.-A.; Org. Lett. **2008**, 10, 2817-2820. (x) Wu, R.; Chang, X.; Lu, A.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Chem. Commun*., 2011, **47**, 5034–5036.
4 (a) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K.; *Adv. Synth. Catal*. **2005**, 347, 1643–1648; (b) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897; (c) Pansare, S. V.; Lingampally, R. *Org. Biomol. Chem.* **2009**, 7, 319–324; (d) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng X.; *Angew. Chem. Int. Ed*. **2009**, 48, 5195–5198; (e) Almasi, D.;

Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem*. **2009**, 74, 6163–6168; (f) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1–22; (g) Thai, K.; Gravel, M. *Tetrahedron–Asymmetr.* **2010**, 21, 751–755; (h) Gomez-Torres, E.; Alonso, D. A.; Gomez-Bengoa, E.; Najera, C. *Org. Lett*. **2011**, 13, 6106–6109; (i) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Celebi-Olcum, N.; Houk, K. N. *Chem. Rev.* **2011**, 111, 5042–5137; (j) Lee, M.; Zhang, L.; Park, Y.; Park, H.-G.; *Tetrahedron* **2012**, 68, 1452–1459; (k) Suez, G,; Bloch, V.; Nisnevich, G.; Gandelman, M.; *Eur. J. Org. Chem*. **2012**, 11, 2118–2122; (l) Shubina, T. E.; Freund, M.; Schenker, S.; Clark, T.; Tsogoeva, S. B. *Beilstein J. Org. Chem.* **2012**, 8*,* 1485–1498; (m) Tang, G.; Gün, U.; Altenbach, H.-J. *Tetrahedron* **2012**, 68, 10230–10235; (n) Sohtome, Y.; Nagasawa, K.; *Org. Biomol. Chem.* **2014**, 12, 1681–1685.

5 (a) Caulkett, P. W. R.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. *J. Org. Chem.* **1999**, 64, 1039–1041; (b) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, 44, 8677–8680.

6 For specific reviews see: (a) *Phase-Transfer Catalysis: Mechanisms and Synthesis;* Halpern, M. E.; American Chemical Society, Washington, DC, **1997**; (b) O'Donnell, M. J. *In Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; pp. 725–755; (c) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, 38, 1583–1585; (d) Shioiri, T. *In Handbook of Phase Transfer Catalysis;* Sasson, Y.; Neumann, R. Ed.; Chapman & Hall: London, **1997**; pp 462–479.

7 [For this reaction and other related PTC alkylations see: (a) O'Donnell, M. J.; Wu, S.; Hoffman, C. *Tetrahedron* **1994**, *50*, 4507–4518; (b) Lygo, B.; Wainwright, P.G. *Tetrahedron Lett.* **1997**, 38, 8595–8598; (c) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett*. **1999**, *40*, 1385–1388; (d) Lygo, B. *Tetrahedron Lett*. **1999**, *40*, 1389–1392; (e) Lygo, B.; Crosby, J.; Lowdon, T.R.; Peterson, J. A.;Wainwright, P.G. *Tetrahedron* **2001**, *57*, 2403-2409; (f) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc*. **1997**, 119, 12414–12415; (g) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347–5350; (h) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000–13001; (i) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

8 Kita, T.; Georgieva, A.; Hashimoto Y.; Nakata, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2032–2034.

9 (a) Lygo, B.; Wainwright, P.G., *Tetrahedron Lett.* **1998**, 39, 1599–1602; (b) Lygo, B.; Wainwright, P.G., *Tetrahedron* **1999**, 55, 6289–6300.

10 Ye, J.; Wang, Y.; Chen, J.; Liang, X., *Adv. Synth. Catal*. **2004**, 346, 691-696.

11 (a) Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. Tetrahedron Lett. **1996**, *37*, 6943–6946. (b) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481–9488.

12 See supporting information for full details.

13 (a) G. Bordwell, *Acc. Chem. Res.*, **1988**, *21*, 3305–3312. (b) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **1967**, *89*, 1721–1725.

14 (a) K. Bowden, *J. Chem. Res. Miniprint*, **1990**, 377. (b) W. K. Warburton and S. J. Angyal, *J. Chem. Soc.*, **1951**, 2492–2494.

15 Alcazar, V.; Moran, J. R.; de Mendoza, J. *Tetrahedron Lett.* **1995**, *36*, 3941–3944.

16 Coffey, D.S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A.; *J. Am. Chem. Soc.*, **2000**, *122*, 4893–4903.